



## **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents**

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## Epidemiology

Human papillomavirus (HPV) infection is the major risk factor for development of cervical cancer,<sup>1,2</sup> the fourth most common cancer in women worldwide.<sup>3,4</sup> Nearly all cervical cancers test positive for HPV genetic sequences,<sup>5-7</sup> most notably the E6 and E7 oncogenes,<sup>8-10</sup> which are thought to play a major role in immortalization of cervical epithelial cells.<sup>11</sup>

Cervical infection with HPV is common and occurs primarily through sexual transmission.<sup>12-16</sup> Penetrative sexual intercourse is not strictly necessary for HPV transmission,<sup>17</sup> but it is the primary risk factor for HPV infection, and HPV prevalence is low in young women who report only non-penetrative sexual contact.<sup>17,18</sup> The vast majority of cervical HPV infections resolve or become latent and undetectable, but in a subset of women, infection persists.<sup>12,19,20</sup> Persistence of oncogenic HPV infection is a necessary step in HPV-related cervical tumorigenesis,<sup>1,21,22</sup> although it appears insufficient for final cell transformation.<sup>11</sup> At least 12 HPV types are considered oncogenic, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.<sup>22-24</sup> HPV68 is considered “probably oncogenic,” and several others are considered “possibly oncogenic.” HPV16 alone, though, accounts for approximately 50% of cervical cancers in the general population and HPV18 for another 10% to 15%. The other oncogenic HPV types each individually account for fewer than 5% of tumors. HPV types 6 and 11 cause 90% of genital warts, but are not considered oncogenic.<sup>22-24</sup>

In the United States and Western Europe, women with HIV/AIDS have significantly higher rates of cervical cancer than women in the general population,<sup>25-31</sup> and recent cohort data show a direct relationship between low CD4 T lymphocyte (CD4) cell count and cervical cancer risk.<sup>32</sup> In Africa, the data are more limited and inconsistent,<sup>33</sup> but prospective registry-based study found increased risk of cervical cancer in women with HIV/AIDS.<sup>34</sup> HIV infection and low CD4 cell count also have been consistently and strongly associated with HPV infection itself and with precancerous cervical lesions, including low-grade cervical intraepithelial neoplasia (CIN), and the precursor to cervical cancer, CIN 3.<sup>35-47</sup> Higher rates of HPV infection and CIN are seen in adolescents with HIV, regardless of whether HIV was acquired vertically or horizontally.<sup>36,48,49</sup> Brogly and colleagues reported that 30% of female adolescents infected with HIV during the perinatal period had an abnormality (e.g., atypical squamous cells of uncertain significance [ASC-US] or greater) on their first Pap test; genital warts were also common in this group, with a cumulative rate of 12% by age 19.

Other cancers caused by HPV include most anal cancers and a subset of tumors of the vulva, vagina, penis, oral cavity, and oropharynx.<sup>1,23,50-52</sup> HPV16 is the type present in most HPV-positive non-cervical cancers.<sup>1,23,50,53,54</sup> Patients with HIV/AIDS also have significantly elevated incidence of these tumors relative to the general population,<sup>25,55,56</sup> and CD4 cell count has been related to risk of anal cancer.<sup>32</sup> Furthermore, high-grade anal intraepithelial neoplasia (AIN), the likely anal cancer precursor lesion, is more common in HIV-seropositive adults and adolescents than in HIV-seronegative adults and adolescents,<sup>57-59</sup> as are anal and genital warts, and in women, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).<sup>60-62</sup>

Despite the associations between HIV and CD4 cell count with HPV-related cancers and precancers, the impact of antiretroviral therapy (ART) on the incidence of HPV-related tumors is uncertain, and it is possible that the impact differs by tumor type. Some studies found decreased persistence/progression of CIN with ART,<sup>63</sup> including a study that distinguished between adherence and non-adherence to ART.<sup>64</sup> Incidence of cervical cancer itself, however, has not changed significantly since ART was introduced,<sup>55</sup> but anal cancer incidence appears to have increased.<sup>55</sup> Use of ART did not affect CIN rates in adolescents with perinatally or horizontally acquired HIV.<sup>36,49</sup> The incidence of high-grade VIN was not reduced with ART use, even though rates of low-grade vulvar lesions and anal or genital warts did decrease with ART,<sup>60</sup> and some<sup>65,66</sup> but not other<sup>67,68</sup> studies reported increased rates of oral warts following ART initiation. The burden of HPV-related cancers can be expected to increase in HIV-seropositive patients, given successful prolongation of life with

use of ART for HIV suppression, potentially longer duration of HPV persistence, and accumulation of somatic mutations and epigenetic changes that contribute to carcinogenesis. This clinical scenario may be of particular concern for HPV-related cancers, such as anal cancers, that are not currently subject to routine screening. However, increasing use of HPV vaccination in adolescents and young adults may begin to reduce the risk of HPV-associated cancers in HIV-infected persons in later life.

## Clinical Manifestations

The principal clinical manifestations of mucosal HPV infection are genital, anal, and oral warts; CIN; VIN; VAIN; AIN; anogenital squamous cell cancers; and cervical adenocarcinomas. A subset of oropharyngeal cancers are also caused by HPV.<sup>69</sup>

Oral, genital (condyloma acuminata), and anal warts are usually flat, papular, or pedunculated growths on the mucosa or epithelium. The lesions may measure a few millimeters to 1 to 2 cm in diameter. Most warts are asymptomatic, but warts can be associated with itching or discomfort. In cases associated with more severe immunosuppression, marked enlargement may cause dyspareunia or dyschezia. Lesions of any size may cause cosmetic concerns.

Intraepithelial neoplasias (CIN, VIN, VAIN, and AIN) are often asymptomatic but may manifest with bleeding or itching. Related cancers may also be asymptomatic or may manifest with bleeding, pain, odor, or a visible/ palpable mass. External lesions may be visible or palpable. Similarly, squamous cell cancers at these sites also can be asymptomatic or may manifest with bleeding, pain, or a visible/palpable mass.

## Diagnosis

### *Warts/Condyloma*

Diagnosis of genital and oral warts is made by visual inspection and can be confirmed by biopsy, although biopsy is needed only if the diagnosis is uncertain, the lesions do not respond to standard therapy, or warts are pigmented, indurated, fixed, bleeding, or ulcerated. No data support the use of HPV testing for screening, diagnosis or management of visible genital/oral warts or oral HPV disease in HIV-infected patients.<sup>70</sup>

### *Cervical Neoplasia*

The same cytology (Pap test), and colposcopic techniques with biopsy are used to detect CIN among HIV-seronegative and HIV-seropositive patients (see section on Preventing Disease). At the time of cytology screening, the genitalia and anal canal should be inspected carefully for visual signs of warts, intraepithelial neoplasia, or invasive cancer.

### *Anal and Vulvar/Vaginal Neoplasia*

AIN, VAIN, and VIN are recognized through visual inspection, including high-resolution anoscopy, colposcopy, and biopsy as needed. A digital examination of the anal canal to feel for masses should be performed as part of routine evaluation.

## ***Cervical Cancer Screening Recommendations***

Available HPV tests can detect up to 14 oncogenic HPV types in clinical specimens and are sensitive for the detection of cervical cancer precursors.<sup>71-73</sup> Some commercially available HPV tests will specify whether the oncogenic HPV includes genotypes HPV16 or HPV16/18. The available tests for oncogenic HPV have been incorporated into the screening algorithms. **Note:** HPV testing is always for oncogenic HPV types only; there is no role in testing for non-oncogenic HPV.

Possible Pap test results include:

- Normal (negative for intraepithelial lesion or malignancy)
- LSIL (low-grade squamous intraepithelial lesion) or CIN1 (cervical intraepithelial neoplasia grade 1)

- HSIL (high-grade squamous intraepithelial lesion) or CIN2, 3 (cervical intraepithelial neoplasia grade 2,3)
- ASCUS (Atypical squamous cells of undetermined significance)
- ASC-H (Atypical squamous cells, cannot rule out a high grade lesion)
- AGC (Atypical glandular cells)

## HIV-Infected Women Aged <30 years

### *Screening*

The Pap test is the primary mode for cervical cancer screening for HIV-infected women <30 years. Screening for these women should commence within 1 year of the onset of sexual activity regardless of mode of HIV transmission (e.g., sexual activity, perinatal exposure) but no later than 21 years old. HIV-infected women 21 to 29 years old should have a Pap test at the time of initial diagnosis with HIV. Provided the initial Pap test for young (or newly diagnosed) HIV-infected woman is normal, the next Pap test should be in 12 months (**BII**). Some experts recommend a Pap test at 6 months after the baseline test (**CIII**). If the results of the 3 consecutive Pap tests are normal, follow up Pap tests should be every 3 years (**BII**). Co-testing (Pap test and HPV test) is not recommended for HIV-infected women <30 years of age.

### *Abnormal Pap Test Results*

For ASC-US Pap test, if reflex HPV testing is positive, a referral to colposcopy is recommended. If HPV testing is not available or not done, then repeat cytology in 6 to 12 months is recommended (**AII**). For any result equal to or greater than ASC-US on repeat cytology, referral to colposcopy is recommended (**AII**).

For LSIL or worse (including ASC-H, AGC and HSIL) referral to colposcopy is recommended (regardless of reflex HPV result, if done).

### *Rationale*

These recommendations reflect evidence that HIV-infected women <21 years of age and sexually active may have a high rate of progression of abnormal cytology<sup>36</sup> (**BII**). No similar prospective data are available for adolescents infected during the perinatal period, but as noted earlier, Brogly and colleagues reported that 30% of such adolescents had ASC-US or greater on their first cervical Pap test.<sup>49</sup> The mean age at the time of the first Pap test was 16.7 years, with a range of 13 to 23 years.

Because of the relatively high HPV prevalence before age 30, HPV co-testing is not recommended for HIV-uninfected women in this age group.

## HIV-Infected Women Aged ≥30 years

Cervical cancer screening in HIV-infected women should continue throughout a woman's lifetime (and not, as in the general population, end at 65 years of age). Either Pap testing only or Pap testing and HPV co-testing is acceptable for screening.

### *Pap Testing Only*

If screening with Pap tests alone, the HIV-infected woman should have a Pap test at the time of HIV-diagnosis (baseline), then every 12 months (**BII**). Some experts recommend a Pap test at 6 months after the baseline test (**CIII**). If the results of the 3 consecutive Pap tests are normal, follow-up Pap tests should be every 3 years (**BII**).

### *Pap and HPV Co-Testing*

If co-testing with Pap and HPV is available, then co-testing can be done at the time of diagnosis or age 30. (**BII**). Co-test negative women (i.e., a normal Pap and negative HPV test) can have their next cervical cancer screening in 3 years.

Those who are Pap test normal but positive for HPV should have repeat co-testing in one year (unless genotype testing for 16 or 16/18 is positive). If either of the co-tests at one year is abnormal (i.e., abnormal cytology or positive HPV), referral to colposcopy is recommended.

If the initial HPV results identify HPV16 or HPV16/18, then referral to colposcopy is recommended. If the HPV testing is positive, but the genotype specific testing for HPV16 or HPV 16/18 is negative, then repeat co-testing in one year is recommended. If either of the co-tests at one year is abnormal (i.e., abnormal cytology or positive HPV), referral to colposcopy is recommended.

#### *Abnormal Pap Test Results*

For ASC-US Pap test, if reflex HPV testing is positive, then referral to colposcopy is recommended. If HPV testing is not available, repeat cytology in 6 to 12 months is recommended (**AII**). For any result  $\geq$  ASC-US on repeat cytology, referral to colposcopy is recommended (**AII**).

For LSIL or worse (including ASC-H, AGC and HSIL) referral to colposcopy is recommended (regardless of HPV result, if done).

#### *Rationale*

Current guidelines from both the American Cancer Society and the U.S. Preventive Services Task Force allow for use of HPV co-testing with cytology. A negative HPV test predicts prolonged low risk of cancer. Cytology/HPV co-testing can allow for a prolonged cervical cancer screening interval in HIV-infected women who are older than age 29 and have normal cervical cytology with concurrent negative HPV testing.<sup>74,75</sup>

## **Preventing HPV Infection**

### ***HPV Vaccine***

There are three FDA-approved HPV vaccines: bivalent, quadrivalent, and 9-valent. All three vaccines prevent HPV16 and HPV18 infections and prevent pre-cancers (and likely cancers) caused by HPV types 16 and 18. The quadrivalent and 9-valent HPV vaccines also prevent HPV6 and HPV11 infections and genital warts due to these types. The 9-valent vaccine also prevents infection and precancers due to 5 additional types, HPV 31, 33, 45, 52, and 58.

Clinical trials of all three vaccines have demonstrated high efficacy for prevention of cervical precancer due to vaccine types in women.<sup>76-78</sup> Clinical trials of the quadrivalent HPV vaccine have also demonstrated high efficacy for prevention of vaginal and vulvar precancer in women. The quadrivalent vaccine has been shown to prevent anal HPV6/11/16/18 infections, AIN and external genital lesions related to these types.<sup>79-82</sup>

Although there are no efficacy data with the 9-valent HPV vaccine in men, a clinical trial established the safety of the vaccine in young men aged 16 to 26 and showed similar antibody concentrations as a young women aged 16 to 26 in whom efficacy was established.<sup>83</sup> The CDC Advisory Committee on Immunization Practices has recommended routine vaccination with any HPV vaccines for 11- or 12-year-old girls.<sup>84,85</sup> The vaccine series can be started at age 9. Catch-up vaccination is recommended for 13- to 26-year-old females who have not been vaccinated (**AI**). All 3 HPV vaccines should be delivered through a series of 3 intramuscular injections over a 6-month period. The second and third doses should be given at 1 to 2 months and then 6 months after the first dose. The Advisory Committee also recommended routine quadrivalent or 9-valent HPV vaccination of males aged 11 to 12 years in the general population, with catch-up vaccination up to age 21 (**AI**). Vaccination was also recommended for males aged 22 to 26 years who are immunocompromised, MSM, or who test positive for HIV infection.<sup>84,86</sup>

No studies have been completed on the efficacy of HPV vaccination against infections or related disease in HIV-infected individuals. However, several studies have been completed on the safety and immunogenicity of the bivalent and quadrivalent vaccines<sup>87,88</sup> in HIV-infected individuals.



The studies have demonstrated that these vaccine are safe and immunogenic in a broad range of HIV-infected groups. No data are available on the safety and immunogenicity of the 9-valent vaccine in HIV-infected populations. Some studies demonstrated antibody levels lower in HIV-infected individuals compared to those who are uninfected, however, the clinical significance of this observation is unknown.

A randomized clinical trial of quadrivalent HPV vaccine found the vaccine to be safe and immunogenic in HIV-infected children aged >7 to <12 years;<sup>87</sup> albeit type-specific antibody levels were less for HPV 6 and 18 compared to age-matched historic HIV-uninfected controls.<sup>87</sup> A long term follow-up study of these children found the vaccine to be safe and immunogenic in children aged 7 to 12 years; after 72 weeks, ≥94% had antibodies to HPV 6, 11, and 16, but only 76% had antibodies to HPV18.<sup>89</sup> In this study, after a fourth dose, all children demonstrated an anamnestic response to all HPV vaccine types. A study of the quadrivalent HPV vaccine in HIV-infected males aged 21 to 67 years found the vaccine to be immunogenic to all 4 HPV types and well tolerated.<sup>88</sup> A study of the quadrivalent HPV vaccine in HIV-infected females aged 13 to 45 years (mean age 36) found the vaccine to be immunogenic to all 4 HPV types. However, seroconversion proportions were higher among women with baseline CD4 cell counts >200 cells/μL compared with ≤200 cells/μL.<sup>90</sup> In a study of the bivalent HPV vaccine comparing antibody response in HIV-infected and HIV-uninfected females aged 18 to 25 years<sup>91</sup> all subjects seroconverted to HPV16 and 18 and the vaccine was well tolerated but geometric mean titers were lower in the HIV-infected females compared with those who were HIV-uninfected.

The 9-valent HPV vaccine targets more HPV types associated with cancer than bivalent or quadrivalent HPV vaccines. The additional 5 high-risk HPV types covered by the 9-valent vaccine were found in 4.2% to 18.3% of HPV-associated anogenital cancers depending on location in U.S. men and women.<sup>92</sup> Overall, 4% of HPV associated cancers in males and 14% of HPV associated cancers in females in the US are estimated to be due to these additional 5 types.

HPV vaccination is recommended for HIV-infected girls and boys aged 9 through 12 years **(AIII)**. Ongoing studies are evaluating the efficacy and duration of immune response in HIV-infected boys and girls. Because the HPV vaccines work to prevent initial HPV infection, administration ideally should precede sexual exposure to HPV. Because some HIV-infected individuals have had many sex partners prior to vaccination, the vaccines may be of less benefit in these patients than in those with few or no lifetime sex partners. Current data from HIV-infected individuals aged 13 to 26 years on prior exposure to HPV types included in currently available vaccines are insufficient to determine the proportion that would benefit from vaccination. Given existing evidence that the vaccine is safe and immunogenic,<sup>87,88</sup> and because of the potential benefit in preventing HPV-associated disease and cancer in this population, HPV vaccination is recommended for HIV-infected males and females aged 13 through 26 **(BIII)**.

Vaccination is likely to be less effective in HIV-infected men and women aged 19 to 26 than in those who are younger because of the strong possibility that they have already acquired HPV vaccine types through sexual activity. Some experts recommend basing vaccination on a discussion between the patient and health care provider that includes the likelihood of previous HPV exposure and potential benefit of the vaccine **(CIII)**. Data are insufficient to recommend vaccination for those older than age 26, and neither vaccine is approved for use in men or women older than age 26. HIV-infected women who have been vaccinated should also have routine cervical cancer screening because the vaccine does not prevent all HPV types that may be precursors to cervical cancer and because the vaccine may be less effective in HIV-infected women (especially those with low CD4 cell counts) than in HIV-uninfected women.

## ***Condom Use***

The use of male latex condoms is strongly recommended for preventing transmission or acquisition of HPV infection, as well as preventing HIV and other sexually transmitted diseases (STDs) **(AII)**. Latex condoms provide a sufficient barrier to prevent passage of particles the size of HPV.<sup>93</sup> Consistent and proper use of latex male condoms has been associated with 70% lower incidence of oncogenic HPV infection among

women.<sup>18</sup> Similarly, recent cross-sectional data suggested that among heterosexual men, consistent condom use was associated with 50% lower odds of HPV infection of the penis.<sup>94</sup> A meta-analysis found that condom use was associated with reduced risk of genital warts, and in women, with lower rates of CIN.<sup>95</sup> A randomized clinical trial of condom use in heterosexual couples found significantly more frequent clearance of CIN and HPV among women randomized to condom use, and of penile lesions among their male partners.<sup>96,97</sup> In HIV-infected women, several studies have observed lower rates of HPV detection associated with use of condoms.<sup>35,98</sup>

Male condoms have benefits in reducing risk of transmission of nearly all STDs<sup>99</sup> (including HIV infection) during heterosexual intercourse and same-sex intercourse between men. In circumstances when a male condom cannot be used properly, a female condom (e.g., an FC1 or FC2 Female Condom®) should be considered for heterosexual vaginal intercourse (**AII**) and for heterosexual or male same-sex anal intercourse (**BIII**).<sup>100-103</sup> Data on FC1 and FC2 Female Condoms suggest the devices are protective against STDs.<sup>102</sup>

### ***Male Circumcision***

Evidence is growing that male circumcision reduces rates of oncogenic HPV infection of the penis, based on data from randomized clinical trials<sup>104-107</sup> and observational studies.<sup>108-113</sup> Observational studies in the general population also suggest that circumcision is associated with lower risk of penile cancer,<sup>114-117</sup> and of cervical cancer in sexual partners.<sup>118</sup> Relevant data in HIV-seropositive men, however, are limited,<sup>106</sup> and the findings to date suggest that, while protective, the effects of circumcision against HPV infection may be less in HIV-infected than in HIV-seronegative individuals.<sup>106,107</sup> Furthermore, no clinical trials have assessed whether circumcision of HIV-seropositive men reduces risk of genital or anal HPV-related cancer or precancer (such as AIN) or oncogenic HPV infection of the anal or oral mucosa for them or their sexual partners. Evidence is insufficient to recommend adult male circumcision solely for the purpose of reducing the risk of oncogenic HPV infection in HIV-infected men, or their sex partners, in the United States.

## **Preventing Disease**

### ***Preventing Vaginal and Vulvar Cancer***

Following hysterectomy for benign disease, routine screening for vaginal cancer is not recommended for HIV-seropositive women (**AIII**). However, women with a history of high-grade CIN, adenocarcinoma in situ, or invasive cervical cancer are at increased risk and should be followed with an annual vaginal cuff Pap test (**BIII**).<sup>119,120</sup> For patients with an abnormal vaginal cuff Pap test results with no visible vaginal colposcopic abnormalities, the use of Lugol's iodine to stain the vagina is recommended (**AIII**). Vaginal colposcopy also is indicated in the presence of concomitant cervical and vulvar lesions.<sup>121,122</sup> Classification of VAIN parallels that of the cervix, that is, VAIN 1, VAIN 2, and VAIN 3.

No screening procedure is available for vulvar cancer. However, biopsy or referral is indicated when inspection/palpation identifies lesions suspicious for VIN or cancer.

### ***Preventing Anal Cancer***

Some cost-effectiveness evaluations indicate that in HIV-seropositive patients, screening for lesions using anal cytology and treating anal precancerous lesions to reduce risk of anal cancer in HIV-infected patients may provide clinical benefits comparable to measures for prevention of other opportunistic infection.<sup>123-125</sup> AIN lesions are similar in many ways to CIN, but there may be differences in natural history, optimal screening, and treatment approaches to prevent cancer. At this time, no national recommendations exist for routine screening for anal cancer.<sup>70</sup> However, some specialists recommend anal cytologic screening or high resolution anoscopy<sup>125</sup> for HIV-seropositive men and women (**CIII**). An annual digital anal examination may be useful to detect masses on palpation that could be anal cancer (**BIII**).<sup>126</sup> Screening for anal cancer with anal cytology should not be done without the availability of referral for high resolution anoscopy. If anal cytology is performed and indicates ASC-US, then ASC cannot rule out ASC-H, LSIL, or high-grade

squamous intraepithelial lesion (HSIL), then it should be followed by high-resolution anoscopy (**BIII**). Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer (**BIII**) (see section on treatment for details on treating AIN).

## Treating Disease

### *Preferred and Alternative Approaches for Treatment, Including Duration of Therapy*

#### Treating Genital and Oral Warts

HIV-infected patients may have larger or more numerous warts, may not respond as well to therapy for genital warts as individuals who are immunocompetent, and may have more frequent recurrences after treatment.<sup>61,127,128</sup> Genital warts are not life-threatening, and they may regress without therapy, even in patients with HIV, especially when immunity is relatively preserved. Treatments are available for genital warts but none is uniformly effective or uniformly preferred.<sup>70</sup> Lacking randomized clinical trials (RCTs) specific to HIV-infected individuals, guidelines for treatment of STDs in HIV-infected patients should be followed.<sup>70</sup> More than one treatment option may be required for refractory or recurrent lesions in patients with HIV infection. Histologic diagnosis should be obtained for refractory lesions to confirm the absence of high-grade disease. Intra-anal, vaginal, or cervical warts should be treated and managed by a specialist.

Patient-applied treatments are generally recommended for uncomplicated external warts that can be easily identified and treated by the patient. Imiquimod (5% cream), is a topical cytokine inducer that should be applied at bedtime on 3 non-consecutive nights per week, for up to 16 weeks, until lesions are no longer visible. The treatment area should be washed with soap and water 6 to 10 hours after the application (**BII**). Podofilox 0.5% solution or gel should be applied to visible anogenital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, up to four times (**BIII**). Another option is sinecatechins (15% ointment), a topical botanical product that contains active catechins from green tea and should be applied 3 times daily for up to 16 weeks, until warts are completely cleared and not visible (**BIII**).

No clinical trials of this latter treatment option have been conducted in HIV-infected individuals.

Provider-applied treatments such as cryotherapy, trichloroacetic acid (TCA), bichloroacetic acid (BCA), and surgery, are typically recommended for complex or multicentric lesions, lesions inaccessible to patient-applied therapy, or because of patient or provider preference.

Cryotherapy (liquid nitrogen or cryoprobe) destroys lesions by thermal-induced cytolysis and should be applied until each lesion is thoroughly frozen, with treatment repeated every 1 to 2 weeks for up to 4 weeks until lesions are no longer visible (**BIII**). Some specialists recommend allowing the lesion to thaw and freezing a second time in each session (**BIII**).

TCA and BCA (80% to 90%) each act as caustic agents to destroy wart tissue and should be applied to warts only and allowed to dry until a white frosting develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove unreacted acid. The treatment can be repeated weekly for up to 6 weeks, until lesions are no longer visible (**BIII**).

Surgical treatments (e.g., tangential scissor excision, tangential shave excision, curettage, electrosurgery, electrocautery, infrared coagulation) can be used for external genital and anal warts (**BIII**). Laser surgery is an option, but is usually more expensive (**CIII**).

Topical application of cidofovir has reported activity against genital warts (**CIII**), but no topical formulation is commercially available. Intralesional interferon has been used for the treatment of genital warts but because of cost, difficulty of administration, and potential for systemic side effects such as fever, fatigue, myalgias, and leukopenia, it is not recommended for first-line treatment (**CIII**). Podophyllin resin may be an alternative provider-applied treatment, with strict adherence to recommendations on application. It has inconsistent potency in topical preparations, and can have toxicity that may limit routine use in clinical practice.



There is no consensus on optimal treatments of oral warts. Many treatments for anogenital warts cannot be used in the oral mucosa. Given the lack of RCTs, surgery is the most common treatment for oral warts that interfere with function or need to be removed for aesthetic reasons.<sup>129</sup>

### Treating CIN and Cervical Cancer

HIV-infected women with CIN should be managed by a clinician with experience in colposcopy and treatment of cervical cancer precursors. In general, CIN in HIV-infected women should be managed according to ASCCP guidelines.<sup>130</sup>

Women with satisfactory colposcopy and biopsy-confirmed high-grade CIN can be treated with either ablation (i.e., cryotherapy, laser vaporization, electrocautery, diathermy, and cold coagulation) or excisional methods (e.g., loop electrosurgical excision procedure, laser conization, cold knife conization), whereas women with unsatisfactory colposcopy should be treated only with excisional methods (**AII**). In patients with recurrent high-grade CIN, diagnostic excisional methods are recommended (**AII**). Hysterectomy is acceptable for treatment of recurrent or persistent biopsy-confirmed high-grade CIN (**BII**); if invasive disease is suspected, the patient should be managed in consultation with a gynecologic oncologist. For HIV-infected adolescents, the ASCCP guidelines for adolescents and young women should continue to be followed. In these patients, progression of lesions is more common, and so is recurrence. Therefore, close observation, as outlined in the guidelines, should be considered for management of CIN 1, CIN 2, CIN2,3 not otherwise specified, and histologic HSIL in HIV-infected adolescents and women younger than 25 (**BIII**). If compliance is questionable, then it may be preferable to follow the treatment arm of management for CIN 2, CIN2, 3, and HSIL (**BIII**).

Management of invasive cervical, vaginal, and vulvar cancer should follow National Comprehensive Cancer Network (NCCN) guidelines ([http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp)). Although complication and failure rates may be higher in HIV-infected women, standard treatment appears safe and efficacious.

### Treating VIN, Vulvar Cancer, VAIN, and Vaginal Cancer

Low-grade VIN/VAIN (VIN/VAIN1) can be observed or managed as for vulvovaginal warts. Treatment of high-grade VIN/VAIN should be individualized in consultation with a specialist and is dependent upon the patient's medical condition and the location and extent of the disease. Various treatment modalities are available for VIN, including local excision, laser vaporization, ablation, and imiquimod therapy. Treatment options for VAIN include topical 5-fluorouracil (5-FU), laser vaporization with CO2 laser, and excisional procedures with electrosurgical loops or a scalpel excision.

Management of vulvar and vaginal cancer must be individualized in consultation with a specialist, following NCCN guidelines ([http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp)).

### Treating AIN and Anal Cancer

For AIN2-3, no adequate RCTs have been reported and data are insufficient to recommend a specific treatment approach. A RCT was recently initiated to determine if treatment of AIN2-3 reduces the incidence of anal cancer in HIV-infected patients. Definitive guidelines on anal screening and treatment in HIV-infected patients will likely follow from the results of this study. Until then, treatment decisions are based on assessment of the size and location of the lesion and its histologic grade. **All treatment modalities are associated with high rates of recurrence.** Topical treatment options including 5-FU, cidofovir,<sup>131</sup> intra-anal imiquimod, and provider-applied TCA have demonstrated moderate efficacy for treatment of intra-anal AIN.<sup>132</sup> Ablative therapies including infrared coagulation, cryotherapy, laser therapy, and electrocautery/hyfreacator are well tolerated. Repeated ablative treatment or a combination of treatment methods are often required for long-term clearance of AIN2-3.

In a retrospective analysis, infrared coagulation was proven to have moderate efficacy in treatment of AIN2

or 3 in HIV-seropositive patients<sup>133</sup> and it was safe and well tolerated in this population in a prospective AIDS Malignancy Consortium study.<sup>134</sup> No indications exist for systemic chemotherapy or radiation therapy for patients with AIN in the absence of evidence of invasive cancer.

The most commonly used treatment for anal cancer is combination radiation and chemotherapy.

### **Treating HPV-Associated Disease at Other Sites, Including the Penis and Mouth**

Penile and some oropharyngeal cancers are associated with HPV infection. Treatment options do not differ between HIV-infected and HIV-uninfected men and women. Data suggest a more favorable prognosis for HPV-associated oropharyngeal cancers, compared with non-HPV-associated oropharyngeal cancers.<sup>135</sup>

### ***Special Considerations With Regard To Starting ART***

Currently, there are no data to indicate that decisions about initiation of ART should be influenced by presence of HPV-related oral, anal, or genital disease. Some studies have found decreased persistence or progression of CIN during ART,<sup>63</sup> including the only study that distinguished adherent from nonadherent ART use.<sup>64</sup> However, the incidence of cervical cancer itself has not changed significantly since the introduction of ART,<sup>55</sup> and anal cancer incidence appears to have increased.<sup>55</sup> Use of ART did not affect rates of CIN in adolescents with perinatally or horizontally acquired HIV.<sup>36,49</sup> Similarly, use of ART was not associated with a reduced incidence of high-grade vulvar neoplasia but it was associated with lower rates of low-grade vulvar lesions and anal or genital warts.<sup>136</sup> Some,<sup>65,66</sup> but not all, studies<sup>67,68</sup> reported increased rates of oral warts following ART initiation. Study results do not indicate that treatment for CIN or AIN should be modified for patients receiving ART. Conversely, no evidence indicates that ART should be instituted or modified solely for the purpose of treating CIN or AIN, and the diagnosis of CIN or AIN in HIV-infected individuals should not be considered an indication for initiation of ART.

### ***Monitoring Response to Therapy and Adverse Events (Including IRIS)***

Monitoring by physical examination is required during and after treatment of genital warts to detect toxicity, persistence, or recurrence, all of which are common with each of the treatments.

Because recurrences of CIN and cervical cancer after conventional therapy are more common in patients who are HIV-seropositive, they should be followed after treatment with frequent cytologic screening and colposcopic examination, according to published guidelines (**AII**) (see Preventing Disease and Treating sections).<sup>130,137,138</sup> Treatment of CIN with ablative and excisional modalities can be associated with several adverse events, such as pain and discomfort, intraoperative hemorrhage, postoperative hemorrhage, infection, and cervical stenosis; individualized treatment of adverse events is required.

Each of the treatment modalities for AIN described above is associated with adverse events, primarily pain, bleeding, ulceration, and in rare cases, development of abscesses, fissures, or fistulas. Patients can be monitored for adverse events using the methods previously described.

Treatment for anal cancer with combination radiation and chemotherapy is associated with a high rate of morbidity, even when the treatment is successful. The most important complication is radiation-associated proctitis.

### ***Managing Treatment Failure***

For persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered (**AIII**). Biopsy should be considered to exclude VIN. Genital warts often require more than one course of treatment.

Recurrent cytologic and histologic abnormalities after therapy for CIN should be managed according to ASCCP guidelines.<sup>130</sup>

There is no consensus on the treatment of biopsy-proven recurrent VIN and surgical excision can be considered.

## Preventing Recurrence

Monitoring after therapy for cervical disease should follow ASCCP guidelines.<sup>130</sup> In one study of HIV-infected women treated for high-grade CIN, low-dose intravaginal 5-FU (2 g twice weekly for 6 months) reduced the short-term risk of recurrence.<sup>139</sup> Clinical experience with this therapy, however, is too limited to provide a recommendation for use and no follow-up study to confirm these observations has been reported. No guidelines exist regarding frequency of monitoring after therapy for VIN, but twice-yearly vulvar inspection appears reasonable for women who have been treated for VIN. Women who have been treated for high-grade VAIN should be managed like those with CIN2, that is, with cytology at 6 and 12 months after therapy, and annually thereafter.

No indication exists for secondary prophylaxis (chronic maintenance therapy) with any of the conventional modalities to prevent recurrence of genital warts, CIN, or AIN.

## Special Considerations during Pregnancy

HIV-infected pregnant women with genital warts or anogenital HPV-related neoplasia are best managed by an interdisciplinary team of specialists (such as an ob/gyn and an infectious disease physician). Pregnancy may be associated with an increased frequency and rate of growth of genital warts.<sup>140-142</sup> Podofilox should not be used during pregnancy (**BIII**). At present, the evidence is insufficient to recommend imiquimod use during pregnancy (**CIII**). No anomalies have been observed with the use of imiquimod in animals during pregnancy. There have been several case series describing the use of imiquimod during pregnancy also without any significant adverse effects.<sup>143-145</sup>

Other topical treatments (such as BCA and TCA) and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy (**AIII**). Transmission of genital HPV6 and 11 from vaginal secretions at delivery is the presumed mechanism of early-onset recurrent respiratory papillomatosis in children. This condition is rare but is more common among children of women who have genital warts at delivery.<sup>146</sup> Cesarean delivery is not known to prevent this condition in infants and children.<sup>140-142,147</sup> No change in obstetrical management is indicated for women with genital warts unless extensive condylomata are present that might impede vaginal delivery or cause extensive bleeding (**AIII**).<sup>148-151</sup>

Pregnant women should undergo cervical cancer screening as recommended above for non-pregnant women. Cytobrush sampling can be done during pregnancy.<sup>152</sup> Pregnant women with abnormal cervical cytology results should undergo colposcopy and cervical biopsy of lesions suspicious for high-grade disease or cancer (**BIII**). Increased bleeding may occur with cervical biopsy during pregnancy. Endocervical curettage is contraindicated in pregnant women (**AIII**).

Pregnant women with ASC-US can be managed the same as non-pregnant women, although deferral of colposcopy until at least 6 weeks postpartum is recommended (**CIII**). Treatment of CIN is not recommended during pregnancy unless invasive disease is suspected. Pregnant women with suspected cervical cancer should be referred to a gynecologic oncologist for definitive diagnosis, treatment, and development of a delivery plan. Vaginal delivery is not recommended for women with invasive cervical cancer.

For women without suspicion of invasive disease, re-evaluation with cytology and colposcopy is recommended after 6 weeks postpartum. Women with CIN can deliver vaginally.

At present, vaccination with commercially available HPV vaccine **is not recommended** during pregnancy (**CIII**). However, in a combined analysis of 5 RCTs of the HPV6/11/16/18 vaccine, administration of the vaccine to women who became pregnant during the course of the trial did not appear to negatively affect pregnancy outcomes.<sup>153</sup>

The effects of treatment of AIN on pregnancy are unknown. Most experts recommend deferral of diagnosis and treatment of AIN until after delivery unless a strong clinical suspicion of anal cancer exists.

## Recommendations for Cervical Cancer Screening for HIV-Infected Women

### HIV-Infected Women Aged <30 Years:

- If younger than age 21, known to be HIV-infected or newly diagnosed with HIV, and sexually active, screen within 1 year of onset of sexual activity regardless of mode of HIV infection.
- HIV-infected women aged 21–29 should have a Pap test following initial diagnosis.
- Pap test should be done at baseline and every 12 months **(BII)**.
- Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**
- If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years **(BII)**
- Co-testing (Pap test and HPV test) is not recommended for women younger than 30.

### HIV-Infected Women Aged >30 Years

#### *Pap Testing Only:*

- Pap test should be done at baseline and every 12 months **(BII)**.
- Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**.
- If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years **(BII)**.

#### *Or:*

#### *Pap Test and HPV Co-Testing:*

- Pap test and HPV co-testing should be done at baseline **(BII)**.
- If result of the Pap test is normal and HPV co-testing is negative, follow up Pap test and HPV co-testing can be performed every 3 years **(BII)**.
- If the result of the Pap test is normal but HPV co-testing is positive, follow up test with Pap test and HPV co-testing should be performed in one year.
- If the one year follow-up Pap test is abnormal or HPV co-testing is positive, referral to colposcopy is recommended.

### Preventing First Episode of HPV Infection

#### *Indications for HPV Vaccination:*

- HIV-infected; aged 9–26 years **(BIII)**

**Note:** Please refer to Pediatric OI guidelines for vaccination of boys and girls younger than age 13.

### Vaccination Schedules

#### *For Women:*

- HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**, *or*
- HPV recombinant vaccine quadrivalent (Types 6, 11, 16, 18) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**, *or*
- HPV recombinant vaccine bivalent (Types 16, 18) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**

#### *For Men:*

- HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**, *or*
- HPV recombinant vaccine quadrivalent (Types 6, 11, 16, 18) 0.5 mL IM at 0, 1–2, and 6 months **(BIII)**

## Recommendations for Preventing Human Papillomavirus Infections

### Treating Condyloma Acuminata (Genital Warts)

**Note:** HIV-infected patients may have larger or more numerous warts, may not respond as well to therapy for genital warts, and have a higher risk of recurrence after treatment than HIV-negative individuals. More than one treatment option may be required for refractory or recurrent lesions. Intra-anal, vaginal, or cervical warts should be treated and managed by a specialist.

### Patient-Applied Therapy

*For Uncomplicated External Warts that can be Easily Identified and Treated by the Patient:*

- Imiquimod 5% cream: Apply to lesions at bedtime on 3 non-consecutive nights a week and wash the treatment area with soap and water 6–10 hours after application **(BII)**, repeating the cycle until lesions are no longer seen, for up to 16 weeks, *or*
- Sinecatechins 15% ointment: Apply to area 3 times daily for up to 16 weeks, until warts are not visible **(BIII)**.

### Provider-Applied Therapy

*For Complex or Multicentric Lesions, Lesions Inaccessible to Patient-Applied Treatments, or Patient/Provider Preference:*

- Cryotherapy (liquid nitrogen or cryoprobe): Apply until each lesion is thoroughly frozen; repeat every 1–2 weeks for up to 4 weeks until lesions are no longer visible **(BIII)**. Some specialists allow the lesion to thaw, and then freeze a second time in each session **(BIII)**.
- TCA or BCA cauterization: 80% to 90% aqueous solution, apply to warts only and allow the area to dry until a white frost develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove unreacted acid. Repeat treatment weekly for up to 6 weeks until lesions are no longer visible **(BIII)**.
- Surgical excision **(BIII)** or laser surgery **(CIII)** can be performed for external or anal warts.

**Key to Acronyms:** BCA = bichloroacetic acid; HPV = human papillomavirus; IM = intramuscular; OI = opportunistic infection; TCA = trichloroacetic acid

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